

History of AIDS in HIV-Infected Patients Is Associated With Higher In-Hospital Mortality Following Admission for Acute Myocardial Infarction and Stroke

Nwora Lance Okeke,¹ Charles B. Hicks,⁵ Mehri S. McKellar,¹ Vance G. Fowler Jr,^{1,4} and Jerome J. Federspiel^{2,3,4,a}

¹Division of Infectious Diseases, Department of Medicine, and ²Duke Clinical Research Institute, Duke University Medical Center, Durham, ³Department of Health Policy and Management, Gillings School of Global Public Health, and ⁴School of Medicine, University of North Carolina, Chapel Hill, North Carolina; and ⁵Division of Infectious Diseases, Department of Medicine, University of California, San Diego

Background. Although human immunodeficiency virus (HIV)-infected persons are at increased risk for major cardiovascular events, short-term prognosis after these events is unclear.

Methods. To determine the association between HIV infection and acute myocardial infarction (AMI) and stroke outcomes, we analyzed hospital discharge data from the Nationwide Inpatient Sample (NIS) between 2002 and 2012. Multivariable logistic regression was used to evaluate the association between HIV infection and in-hospital death after AMI or stroke.

Results. Overall, 18 369 785 AMI/stroke hospitalizations were included in the analysis. Patients with a history of AIDS were significantly more likely than uninfected patients to die during hospitalization after admission for AMI or stroke (odds ratio, 3.03 [95% confidence interval {CI}, 1.71–5.38] for AMI and 2.59 [95% CI, 1.97–3.41] for stroke). Additionally, patients with AIDS were more likely than HIV-uninfected patients to be discharged to nonhospital inpatient facilities after admission for AMI (OR, 3.14 [95% CI, 1.72–5.74]) or stroke (OR, 1.45; 95% CI, 1.12–1.87). There was a minimal difference in either outcome between HIV-infected patients without a history of AIDS and uninfected patients.

Conclusions. Patients with a history of AIDS were significantly more likely than uninfected patients to die during hospitalization after admission for AMI or stroke. This disparity was not observed when infected patients without a history of AIDS were compared to uninfected patients, implying that preserving immune function may improve cardiovascular outcomes in HIV-infected persons.

Keywords. HIV infection; cardiovascular disease; acute myocardial infarction; stroke, hospital; outcomes.

Cardiovascular disease (CVD) is now one of the leading causes of death in human immunodeficiency virus (HIV)-infected patients in the United States [1–4]. HIV-infected patients are at higher risk for acute myocardial infarction (AMI) than uninfected patients, even after adjustment for traditional CVD risk factors [2–4]. This increased risk of CVD may be linked to the severity of HIV-associated immunosuppression. For example, a recent study found no significant difference in the incidence of AMI among uninfected patients and patients with less advanced HIV infection [3]. By contrast, little is known about the relationship between severity of HIV infection and clinical outcomes in patients with AMI or stroke. The current study examined the in-hospital outcomes of AMI and stroke in patients with a history of AIDS, HIV-infected patients without a history of AIDS, and

uninfected patients. To accomplish this goal, we used the Nationwide Inpatient Sample (NIS), a registry of billing data for >87 million all-payer hospitalizations in the United States.

METHODS

Data Source and Case Ascertainment

Hospital discharge data were obtained from the 2002–2012 NIS, a component of the Healthcare Cost and Utilization Project produced by the Agency for Healthcare Research and Quality. The NIS is an all-payer data set including records for approximately 20% of nonfederal inpatient discharges in the United States [5]. Survey weights are provided with the NIS to enable estimation of national trends in inpatient hospitalizations. Data provided on the NIS include demographic characteristics (age, sex, and race), primary payer, diagnosis and procedure codes, length of stay, discharge disposition, and inpatient charges. Admissions associated with HIV infection were identified on the basis of the presence of *International Classifications of Disease, Ninth Edition, Clinical Modification* (ICD-9-CM) diagnosis code 042 (“human immunodeficiency virus”) and V08 (“asymptomatic HIV”) listed at any position in the claim [6]. The 042 code is reserved for patients who have ever had a documented HIV-related illness or met clinical criteria for AIDS

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^aPresent affiliation: Department of Gynecology and Obstetrics, Johns Hopkins University School of Medicine, Baltimore, Maryland.

Correspondence: N. L. Okeke, Department of Medicine, Division of Infectious Diseases, Duke University Medical Center, Hanes House, Rm 154, 315 Trent Dr, Durham, NC 27710 (lance.okeke@duke.edu).

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and is thus a surrogate indicator of current or prior severe HIV-related immunosuppression. In the current study, patients with a history of AIDS were identified by an ICD-9-CM code of 042, while patients with chronically asymptomatic HIV infection were identified by the ICD-9-CM billing code of V08. All patients with a reported ICD-9-CM diagnosis code of 410.00–410.92 for AMI and of 430.00–434.91 for stroke in either the first or second diagnosis code listed on the claim were identified for inclusion in the analysis. The primary outcome of interest was all-cause in-hospital mortality. Other outcomes of interest were posthospitalization discharge to a nonhospital inpatient facility (ie, a skilled nursing facility, an inpatient rehabilitation facility, a long-term acute care hospital, or an intermediate care facility) and length of hospital stay.

Statistical Analysis

Unadjusted comparisons between patient characteristics and outcomes were calculated using weighted linear and logistic regression. Adjusted associations between HIV status and outcomes were evaluated using weighted logistic, negative binomial, and gamma log-link regressions as appropriate. The data set was constructed using SAS System, version 9.4 (SAS Institute, Cary, North Carolina), with analyses performed using Stata/MP, version 14.0 (StataCorp, College Station, Texas). Reported odds ratios (ORs) were adjusted for a number of patient-level factors, including age, sex, race/ethnicity, insurance status, hospital size, hospital with academic affiliation, urban versus rural hospital, hospital region, tobacco use, substance abuse, and comorbid medical conditions. To more easily evaluate the findings, the adjusted results are also presented as incremental effects. A 2-sided α level of 0.05 was considered statistically significant. Authorization for this study and a waiver of informed consent was obtained from the University of North Carolina–Chapel Hill Institutional Review Board.

RESULTS

AMI Hospitalization Outcomes by HIV Status

Between 2002 and 2012, 8 233 608 AMI hospitalizations and 10 136 177 stroke hospitalizations occurred in the United States, based on weighted estimates of inpatient admissions included in the NIS database (Table 1). Of these hospitalizations, 48 933 had a billing diagnosis code for HIV (21 117 AMI-associated hospitalizations and 27 816 stroke-associated hospitalizations). HIV-infected patients hospitalized for AMI were significantly younger than uninfected patients (51.8 years vs 68.5 years; $P \leq .001$). There was also a higher proportion of black individuals (39.1% vs 9.5%; $P < .001$) and lower proportion of females (19.2% vs 41.3%; $P < .001$) in the HIV-infected group. During the study period, the overall number of hospitalizations for AMI decreased by 12%, but it increased by 21% among patients with a history of AIDS and by 83% among HIV-infected patients without a history of AIDS ($P \leq .001$ for trend; Figure 1).

AMI hospitalizations were longer among patients with a history of AIDS. After adjustment for patient and facility level factors, the duration of AMI-associated inpatient admissions in patients with a history of AIDS was 4.1 days longer than for uninfected patients (95% confidence interval [CI], 2.0–6.3 days; $P < .001$; Figure 2). By contrast, the duration of hospitalizations for AMI for patients without a history of AIDS was shorter (adjusted difference, -0.8 days; 95% CI, -0.6 to -1.0 days; $P < .0001$) than that of uninfected patients. Patients with a history of AIDS were also significantly more likely to be discharged to nonhospital inpatient facilities after hospitalization than uninfected patients (OR, 3.14; 95% CI, 1.72–5.74). However, there was no significant difference in the likelihood of discharge to a nonhospital inpatient facility following hospitalization for AMI among HIV-infected persons without a history of AIDS and uninfected patients (OR, 0.91; 95% CI, .73–1.14). Overall, patients with a history of AIDS hospitalized for AMI were significantly more likely to die during admission than uninfected patients (OR, 3.03; 95% CI, 1.71–5.38; $P < .001$). However, there was no significant difference in the odds of in-hospital death for AMI-associated hospital admissions between HIV-infected persons without a history of AIDS and uninfected patients (OR, 0.80; 95% CI, .63–1.02).

Stroke Hospitalization Outcomes, by HIV Status

HIV-infected patients hospitalized for stroke were significantly younger than uninfected patients admitted for the same diagnosis (age, 51.0 years vs 70.1 years; $P < .001$; Table 1). Similar to AMI-associated hospitalizations, there was also a higher proportion of black individuals (56.8% vs 14.6%; $P < .001$) and a lower proportion of females (19.2% vs 31.3%; $P < .001$) in the HIV-infected group. Although the overall number of stroke hospitalizations increased in the entire population over the study period (2002–2012), the number of stroke hospitalizations increased more rapidly among HIV-infected patients over the study period (Figure 1).

When hospitalized for stroke, patients with a history of AIDS remained in the hospital longer than uninfected patients. After adjustment for patient-level factors, stroke-associated hospitalizations among patients with a history of AIDS were 30% longer than those of uninfected patients (adjusted difference, 1.8 days; 95% CI, .8–2.7 days; $P < .001$; Figure 3). However, stroke-associated hospitalizations among HIV-infected patients without a history of AIDS were actually slightly shorter than those of uninfected patients (adjusted difference, -0.4 days; 95% CI, -0.1 to -0.7 days).

Stroke-associated hospitalizations among patients with a history of with AIDS were also more likely to result in discharge to a nonhospital inpatient facility than those of uninfected patients (OR, 1.45; 95% CI, 1.12–1.87; Table 2). By contrast, HIV-infected persons without a history of AIDS were only slightly more likely to be discharged to nonhospital inpatient care than uninfected patients (OR, 1.11; 95% CI, 1.01–1.23). After adjustment for

Table 1. Demographic and Clinical Characteristics of Persons With Primary Hospital Diagnoses of Acute Myocardial Infarction (AMI) and Cerebrovascular Accident (CVA), Nationwide Inpatient Sample, 2002–2012

Characteristic	AMI-Associated Hospitalizations, by Presence of HIV Code on Claim (n = 1 736 422; Weighted n = 8 233 608)			CVA-Associated Hospitalizations, by Presence of HIV Code on Claim (n = 2 139 851; Weighted n = 10 136 177)		
	No (n = 1 731 608 Weighted n = 8 210 777)	Yes		No (n = 2 133 477; Weighted n = 10 106 142)	Yes	
		History of AIDS (n = 2 443; Weighted n = 11 591)	No History of AIDS (n = 2 371; Weighted n = 11 240)		History of AIDS (n = 2 807; Weighted n = 13 412)	No History of AIDS (n = 3 567; Weighted n = 16 893)
Age, y						
Overall	68.5 ± 14.4	51.7 ± 9.4 ^a	51.9 ± 9.5 ^a	70.1 ± 14.9	52.3 ± 10.7 ^a	49.5 ± 11.0 ^a
≥50 y	7 323 194 (89.2)	6855 (59.1) ^a	6535 (58.1) ^a	9 183 215 (90.9)	8272 (61.7) ^a	8411 (49.8) ^a
Female sex	3 418 078 (41.6)	2258 (19.5) ^a	2114 (18.8) ^a	5 270 547 (52.2)	4264 (31.8) ^a	5208 (30.8) ^a
Race						
White	5 010 877 (77.6)	4423 (44.9) ^a	4439 (44.7) ^a	5 835 978 (72.3)	3165 (26.7) ^a	4215 (28.2) ^a
Black	611 874 (9.5)	3906 (39.6) ^a	3839 (38.7) ^a	1 177 259 (14.6)	6879 (58.0) ^a	8382 (56.0) ^a
Hispanic	462 718 (7.2)	960 (9.7)	1084 (10.9)	600 602 (7.4)	1274 (10.7)	1787 (11.9)
Asian/PI	135 875 (2.1)	32 (0.3) ^a	63 (0.6) ^a	208 805 (2.6)	53 (0.4) ^a	102 (0.7) ^a
Native American	33 808 (0.5)	29 (0.3)	48 (0.5)	37 949 (0.5)	30 (0.3)	83 (0.6)
Other	198 754 (3.1)	562 504 (5.1)	451 (4.5)	212 737 (2.6)	461 (3.9)	399 (2.7)
Primary payer						
Medicare	4 915 146 (60.0)	4027 (34.8) ^a	5124 (45.7)	6 713 155 (66.5)	4752 (35.6) ^a	6025 (35.7) ^a
Medicaid	442 605 (5.4)	2556 (22.1) ^a	2750 (24.5) ^a	666 102 (6.6)	4243 (31.8) ^a	6017 (35.7) ^a
Private	2 173 902 (26.5)	3469 (30.0)	2295 (20.5)	2 083 863 (20.7)	2634 (19.7)	3068 (18.2)
Self-pay	418 839 (5.1)	934 (8.1)	669 (6.0)	375 938 (3.7)	1046 (7.8)	1142 (6.8)
No charge	38 495 (0.5)	156 (1.4) ^a	39 (0.3)	36 808 (0.4)	199 (1.5) ^a	134 (0.8)
Facility size, based on no. of beds						
Small	830 921 (10.2)	804 (7.0)	703 (6.3)	1 070 546 (10.6)	928 (7.0)	1183 (7.0)
Medium	1 968 215 (24.1)	2831 (24.6)	2527 (22.6)	2 364 164 (23.5)	3126 (23.4)	3711 (22.1)
Large	5 376 422 (65.8)	7865 (68.4)	7947 (71.1)	6 624 814 (65.9)	9292 (69.6)	11 888 (70.8)
Hospital geographic region						
Northeast	1 673 022 (20.4)	3400 (29.3)	3233 (28.8)	1 835 246 (18.2)	4047 (30.2)	4343 (25.7)
Midwest	1 901 460 (23.2)	1479 (12.8)	1309 (11.7)	2 391 689 (23.7)	1738 (13.0)	1751 (10.4)
South	3 269 773 (39.8)	5888 (50.8)	4904 (43.6)	4 063 608 (40.2)	6997 (52.2)	8073 (47.8)
West	1 366 523 (16.6)	824 (7.1) ^a	1793 (16.0)	1 815 869 (18.0)	631 (4.7) ^a	2725 (16.1)
Urban hospital facility	7 201 216 (88.1)	11 073 (96.3)	10 768 (96.4)	8 825 329 (87.7)	12 940 (97.0)	16 246 (96.8)
Hospital with teaching affiliation	3 675 357 (45.0)	7415 (64.5) ^a	7306 (65.4) ^a	4 609 401 (45.8)	9013 (67.5) ^a	11 446 (68.2) ^a
Calendar period ^b						
2002–2005	3 117 511 (38.0)	3655 (32.5)	3588 (31.0)	3 429 110 (34.0)	5073 (30.1)	3293 (24.6)
2006–2009	2 919 823 (35.6)	4033 (35.9)	4158 (36.0)	3 697 864 (36.5)	6471 (38.3)	5081 (37.9)
2010–2012	2 173 144 (26.4)	3551 (31.6)	3845 (33.0)	2 985 438 (29.5)	5349 (31.6)	5039 (37.6)
Comorbid condition						
Congestive heart failure	2 601 977(31.7)	1918 (16.5)	2712(24.1)	1 159 431 (11.5)	907 (6.8)	1080 (6.4)
Peripheral vascular disease	783 708 (9.5)	621 (5.4)	577 (5.1)	920 185 (9.1)	690 (5.1)	637 (3.8) ^a
Hypertension	5 244 570 (63.9)	6674 (57.6)	6170 (54.9)	7 340 040 (72.6)	8718 (65.0)	8499 (50.3) ^a
COPD	1 685 308(20.5)	1792 (15.5)	1932 (17.2)	1 488 899 (14.7)	1873 (14.0)	2195 (13.0)
Diabetes	2 598 395 (31.7)	2531 (21.8)	2496 (22.2)	2 957 299 (29.2)	3298 (24.5)	2853 (16.9)
Obesity	713 065 (8.7)	458 (3.9)	397 (3.5)	552 971 (5.5)	428 (3.2)	263 (1.6) ^a
Alcohol abuse	205 938 (2.5)	613 (5.3)	613 (5.5)	321 315 (3.2)	941 (7.0)	1277 (7.6)
Substance abuse	137 766 (1.7)	2008 (17.3) ^a	2177 (19.4) ^a	162 865 (1.6)	2310 (17.2) ^a	3165 (18.7) ^a
Current smoker	1 534 799 (18.6)	4755 (41.0) ^a	3239 (28.8)	1 222 506 (12.1)	3259 (24.3)	3406 (20.2)
Former smoker	707 272 (8.3)	782 (6.7)	735 (6.5)	765 153 (7.6)	635 (4.7)	632 (3.7)
Hyperlipidemia	885 542 (10.8)	1 394 (12.0)	905 (8.0)	1 016 958 (10.1)	853 (6.4)	592 (3.5) ^a

Data are no. (%) of hospitalizations or mean value ±SD.

Abbreviations: COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; PI, Pacific Islander.

^a Statistically and practically significantly different from the uninfected group ($P < .001$ and Cohen $d > 0.5$, respectively).

^b Percentages represent the proportion of total hospitalizations that occurred in the designated period.

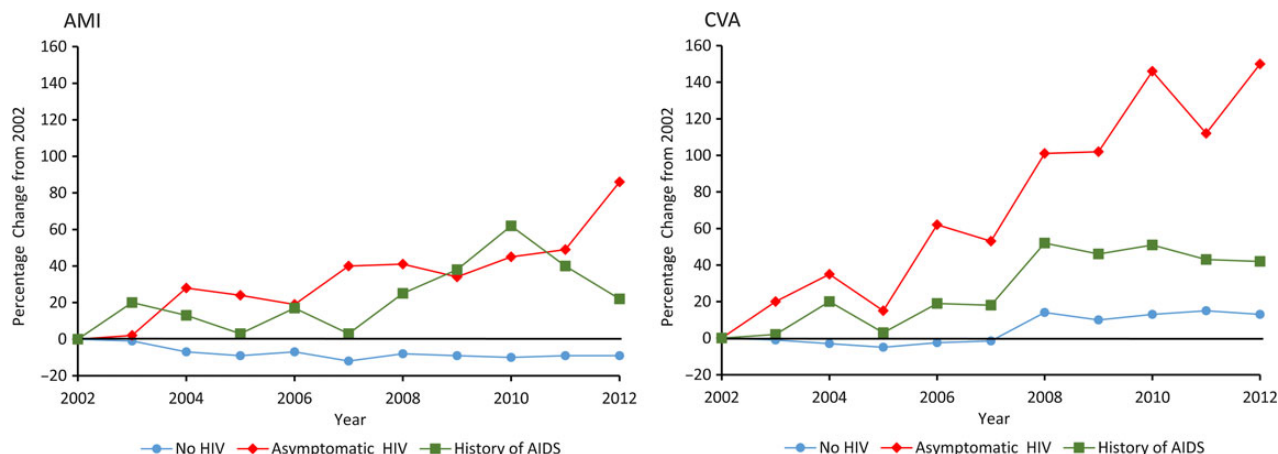


Figure 1. Trends in hospitalizations for acute myocardial infarction and cerebrovascular accident, by human immunodeficiency virus (HIV) claim code, Nationwide Inpatient Sample, 2002–2012. Abbreviations: AMI, acute myocardial infarction; CVA, cerebrovascular accident.

risk factors, patients with a history of AIDS had a significantly higher risk for in-hospital mortality after a stroke than uninfected patients (OR, 2.59; 95% CI, 1.97–3.41; $P < .001$). Similar to our observations for AMI, there was no significant difference in the likelihood of in-hospital mortality after stroke between infected patients without a history of symptomatic disease and uninfected patients (OR, 1.14; 95% CI, .98–1.33).

DISCUSSION

This study documents an association between a history of HIV-induced immunosuppression and outcomes of major CVD events. Patients with a history of AIDS who were hospitalized for either AMI or stroke had a significantly higher risk of in-hospital mortality, a significantly higher likelihood of discharge to nonhospital inpatient facilities, and a significantly longer length of stay than uninfected patients. By contrast, the outcomes of HIV-infected patients without a history of AIDS were similar to those of uninfected patients. This observation

is important because CVD is now one of the leading causes of death among patients with chronic HIV infection and because antiretroviral therapy can dramatically improve HIV-induced immunosuppression [7]. These findings are also timely given the results of the recently published Strategic Timing of Antiretroviral Therapy trial, which indicate that even mild levels of HIV-induced immunosuppression (eg, a $CD4^+$ T-cell count of 350 cells/mm³) adversely affects risk for non-AIDS-related outcomes [8].

Our study increases the understanding of non-AIDS-related clinical consequences of chronic HIV infection. We found that HIV-infected patients who developed AMI or stroke were more than twice as likely to die during hospitalization as uninfected patients with the same CVD event and that most of this mortality risk was borne by patients with a history of AIDS. Clarifying the disproportionate distribution of CVD-associated risk among HIV-infected patients is important because of the growing overlap between the 2 epidemics. Given that over half of

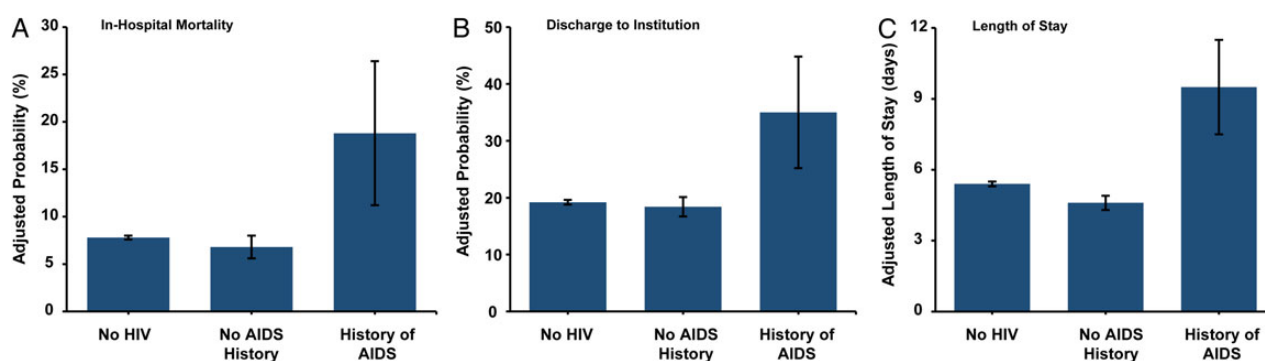


Figure 2. Adjusted values for major outcome metrics for acute myocardial infarction–associated hospitalizations, by human immunodeficiency virus (HIV) diagnosis code, Nationwide Inpatient Sample, 2002–2012. All point estimates were adjusted for age, sex, race/ethnicity, insurance status, hospital size, hospital with academic affiliation, urban versus rural hospital, hospital region, tobacco use, substance abuse, and comorbid medical conditions.

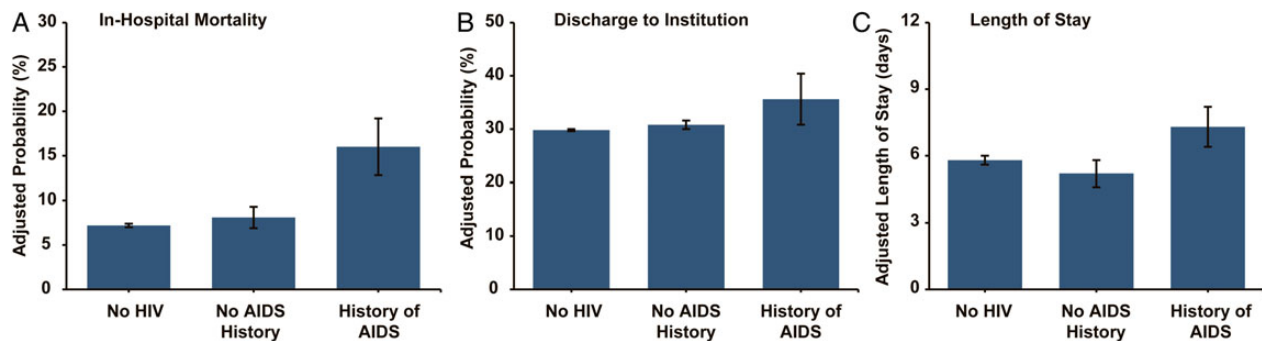


Figure 3. Adjusted values for major outcome metrics for stroke-associated hospitalizations, by human immunodeficiency virus (HIV) diagnosis code, Nationwide Inpatient Sample, 2002–2012. All point estimates were adjusted for age, sex, race/ethnicity, insurance status, hospital size, hospital with academic affiliation, urban versus rural hospital, hospital region, tobacco use, substance abuse, and comorbid medical conditions.

HIV-infected patients living in the United States will be aged ≥ 50 years by 2017 [9], the number of HIV-infected patients with CVD will continue to climb. The precipitous increase in the number of hospitalizations for AMI and stroke among HIV-infected patients over the study period (Figure 1) are a likely manifestation of the rapid aging of this population [10]. Thus, there is an urgent need to improve our understanding of CVD in this population.

Exposure to HIV-induced immunosuppression has been linked to an increased risk of many non-AIDS-related conditions [11–14]. Nadir CD4⁺ T-cell counts of ≤ 350 cells/mm³ are associated with surrogates of atherosclerosis [15,16], including increased carotid intima-media thickness and decreased arterial compliance (indicated by flow-mediated dilatation). Low nadir CD4⁺ T-cell counts have also been associated with increased levels of the inflammatory marker interleukin 6 [17], sustained hypertension, and left ventricular hypertrophy [18,19]. These findings of adverse vascular physiology associated with severe HIV-induced immunosuppression appear to corroborate with published clinical experience. For example, 2 large studies of the Northern California Kaiser Permanente

cohort showed that HIV-infected patients with a CD4⁺ T-cell count of ≤ 200 cells/mm³ had a 74% higher incidence of AMI and a 60% higher incidence of stroke than uninfected patients. Interestingly, there was no significant difference between the incidence rate of AMI and stroke in HIV-infected cohort members with nadir CD4⁺ T-cell counts of ≥ 500 cells/mm³ and uninfected patients [3,20]. The current study provides a key finding by linking the prognosis of HIV-infected patients with AMI or stroke to the patient's level of HIV-associated immunosuppression.

In 2012, the Department of Health and Human Services recommended treatment of all HIV-infected persons regardless of CD4⁺ T-cell count, a recommendation adopted by the World Health Organization in September 2015 [21,22]. With full implementation of these guidelines, one can anticipate that more HIV-infected persons will initiate ART before the onset of advanced HIV-related immunosuppression and the deleterious implications on cardiovascular health associated with it. Our analysis presents evidence supporting the suggestion that the implementation of these guidelines alone will greatly improve AMI-related and stroke-related mortality among HIV-infected

Table 2. Adjusted Estimates for Major Hospitalization Outcome Metrics in Patients Hospitalized for Acute Myocardial Infarction (AMI) and Cerebrovascular Accident (CVA), by Human Immunodeficiency Virus (HIV) Status, Nationwide Inpatient Sample, 2002–2012

HIV Status, by Outcome	Death, OR ^a (95% CI)	Nonhospital Institutional Care, OR ^a (95% CI)	Length of Stay Ratio ^b (95% CI)
AMI-associated hospitalization			
History of AIDS	3.03 (1.71–5.38) ^c	3.14 (1.72–5.74) ^c	1.76 (1.41–2.19) ^c
HIV without history of AIDS	0.80 (.63–1.02)	0.91 (.73–1.14)	0.85 (.82–.88) ^c
CVA-associated hospitalization			
History of AIDS	2.59 (1.97–3.41) ^c	1.45 (1.12–1.87) ^c	1.31 (1.15–1.48) ^c
HIV w/o history of AIDS	1.14 (.98–1.33)	1.12 (1.01–1.23) ^c	0.93 (.87–.99) ^c

All point estimates were adjusted for age, sex, race/ethnicity, insurance status, hospital size, hospital with academic affiliation, urban versus rural hospital, hospital region, tobacco use, substance abuse, calendar year, and comorbid medical conditions.

Abbreviations: CI, confidence interval; CVA, cerebrovascular accident; HIV, human immunodeficiency virus; OR, odds ratio.

^a Reference is no HIV infection.

^b Reference is length of stay for uninfected patients with a diagnosis.

^c Statistically and practically significantly different from the uninfected group ($P < .001$ and Cohen $d > 0.5$, respectively).

patients in the years ahead. At the very least, our study adds to the growing body of evidence that CVD in infected persons without a history of AIDS (ie, those with preserved immune function) may be more similar to CVD in uninfected patients than previously recognized.

Our study has limitations. The use of billing codes renders our data subject to the accuracy of local billing practices of individual health systems. However, the size of our registry (>18 million hospitalizations) likely addresses the influence of severe outliers. Owing to the use of billing data, we are also unable to differentiate between hospitalizations that occurred in patients with active AIDS and asymptomatic patients with a history of AIDS. We also did not have access to CD4⁺ T-cell count, HIV-1 load, or treatment status (or history or antiretroviral exposure) at the time of hospitalization. Although data on longitudinal CD4⁺ T-cell counts were not available for purposes of this analysis, given the association between AIDS and low CD4⁺ T-cell counts, we believe that the billing code for AIDS is a surrogate for a low nadir CD4⁺ T-cell count, and we can postulate that patients with a billing code for AIDS had lower nadir CD4⁺ T-cell counts than patients with a billing code for HIV infection overall. We also acknowledge that, although admission rates per population would be better indicator of population-adjusted hospitalization rates, obtaining an exact enumeration of HIV-infected persons in the United States (and persons with AIDS) at any given time point is not feasible. Finally, we did not have access to indicators of patient acuity on presentation, and thus a potential confounder related to inpatient prognosis was not addressed by our analysis.

In summary, our study demonstrates that patients with a history of AIDS hospitalized for AMI or stroke have a longer inpatient length of stay, are more likely to be discharged to nonhospital inpatient care, and are significantly more likely to die while hospitalized than uninfected patients. By contrast, there is no significant difference in AMI- and stroke-associated hospital outcomes between HIV-infected persons without a history of AIDS and uninfected patients. Future studies are needed to confirm these findings and to better understand their biological basis. In the meantime, our data add further support for the importance of early initiation of antiretroviral therapy in improving non-AIDS-related outcomes in patients living with HIV.

Notes

Acknowledgments. The Nationwide Inpatient Sample is a product of the Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality, in collaboration with partner organizations listed at <http://www.hcup-us.ahrq.gov/db/hcupdatapartners.jsp>.

J. J. F. and N. L. O. had full access to all of the study data and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclaimer. None of the funding agencies had any role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

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Potential conflicts of interest. V. G. F. reports the following activities and compensation: serving as chair of the scientific advisory board for Merck V710; serving as a consultant for Pfizer, Novartis, Galderma, Novadigm, Durata, Debiopharm, Genentech, Achaogen, Affinium, Medicines, Cerexa, Tetrphase, Trius, MedImmune, Bayer, Theravance, Cubist, Basilea, and Affinergy; receipt of grants by his institution or having grants pending from the National Institute Health, MedImmune, Forest/Cerexa, Pfizer, Merck, Advanced Liquid Logics, Theravance, Novartis, and Cubist; receiving royalties from UpToDate; and receiving payment from Green Cross, Cubist, Cerexa, Durata, and Theravance for development of educational presentations, outside the submitted work. V. G. F. also has a patent pending involving diagnostics. C. B. H. is on scientific advisory boards for Bristol-Myers Squibb, Gilead Sciences, Janssen Virology, Merck, and ViiV and has received royalty fees from UpToDate and editorial fees from the Massachusetts Medical Society/Journal Watch. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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